

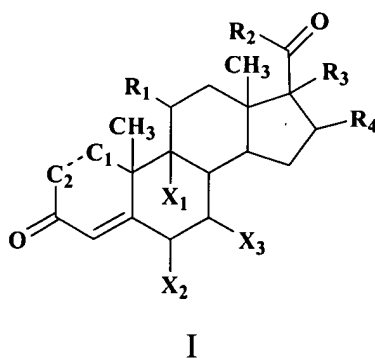
AMENDMENTS TO THE CLAIMS

Kindly amend claim 12 and cancel claims 13, 26, and 27 as provided in the following Claims Listing.

Claims Listing:

Claims 1-11 (cancelled).

12. (currently amended) A method of treating for therapeutic purposes a mammal suffering from an autoimmune or inflammatory condition, said method comprising administering to said mammal a corticosteroid conjugate comprising a corticosteroid attached via a linker to ~~a group that is either~~ a bulky group of greater than 400 daltons ~~or a charged group of less than 400 daltons~~ in an amount effective to treat said condition, said corticosteroid conjugate (i) having anti-inflammatory activity *in vivo*, (ii) having reduced activity in the central nervous system in comparison to said corticosteroid without said group, and (iii) being resistant to *in vivo* cleavage, such that *in vivo* less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion, wherein said corticosteroid is described by formula I:



wherein

the bond between C₁ and C₂ is a double or a single bond;

X₁ represents -H or a halogen atom;

X₂ represents -H, -CH₃, or a halogen atom;

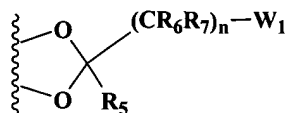
X₃ represents -H or a halogen atom;

R₁ represents =O or -OH;

R₂ represents -CH₃, -SCH₂F, -CH₂Cl, -CH₂-G, -CH₂OH, -CH₂O-P(O)(O⁻)₂, CH₂O-acyl, -CH₂NH-G¹, -CH₂S-G¹, or -CH₂O-G¹;

R₃ and R₄ each, independently, represents -H, C₁₋₁₀ alkyl, -OH, -O-acyl, -O-G¹, or

R₃ and R₄ combine to form a cyclic acetal of formula II wherein:



n is an integer from 0 to 6;

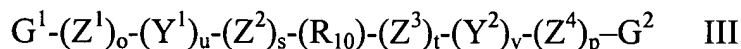
R₅, R₆, and R₇ each, independently, represents -H or C₁₋₁₀ alkyl;

W₁ represents -H, -CH₃, -G¹, -NR₈-G¹, -NH-NH-G¹, -O-G¹, -S-G¹, or -C(O)-G¹, or ~~C(S)-G¹~~;

R₈ represents -H, C₁₋₁₀ alkyl or C₅₋₁₀ aryl; and

G¹ is a bond between said corticosteroid and said linker;

and wherein said linker is described by formula III:



wherein

G¹ is a bond between said corticosteroid and said linker;

G² is a bond between said linker and said bulky group ~~or between said linker and said charged group~~;

Z¹, Z², Z³, and Z⁴ each, independently, is selected from O, S, and NR₁₁;

R₁₁ is hydrogen or a C₁₋₁₀ alkyl group;

Y¹ and Y² are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

o, p, s, t, u, and v are each, independently, 0 or 1; and

R_{10} is a C_{1-10} alkyl, a linear or branched heteroalkyl of 1 to 10 atoms, a linear or branched C_{2-10} alkene, a linear or branched C_{2-10} alkyne, a C_{5-10} aryl, a cyclic system of 3 to 10 atoms, $-(CH_2CH_2O)_qCH_2CH_2-$ in which q is an integer of 1 to 4, or a chemical bond linking $G^1-(Z^1)_o-(Y^1)_u-(Z^2)_s-$ to $-(Z^3)_t-(Y^2)_v-(Z^4)_p-G^2$; and

(a) said corticosteroid and said linker are connected via a first linkage group, and
(b) said linker and said bulky group are connected via a second linkage group, each of
said first linkage group and said second linkage group selected, independently, from an
amine, amide, hydrazide, or thioether linkage;

and wherein said condition is selected from asthma, psoriasis, eczema, organ/tissue
transplant rejection, graft vs. host reactions, Raynaud's syndrome, autoimmune
thyroiditis, Grave's disease, autoimmune hemolytic anemia, autoimmune
thrombocytopenia purpura, mixed connective tissue disease, idiopathic Addison's disease,
Sjogren's syndrome, urticaria, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-
dependent diabetes mellitus, uveitis, Crohn's disease, ulcerative colitis, lupus, tendonitis,
bursitis, adult respiratory distress syndrome, shock, oxygen toxicity, glomerulonephritis,
vasculitis, reactive arthritis, necrotizing enterocolitis, Goodpasture's syndrome,
hypersensitivity pneumonitis, glomerulonephritis; encephalomyelitis, and meningitis.

13. (cancelled).

14. (original) The method of claim 12, wherein said condition is rheumatoid arthritis or colitis.

15. (original) The method of claim 12, wherein said corticosteroid conjugate is administered by intravenous, intraperitoneal, subcutaneous, ocular, topical, nasal, or intramuscular administration.

Claims 16-21 (cancelled).

22. (previously presented) The method of claim 12, wherein said corticosteroid conjugate comprises a corticosteroid attached to a bulky group and said bulky group comprises a naturally occurring polymer or a synthetic polymer.

23. (previously presented) The method of claim 22, wherein said bulky group comprises a glycoprotein, a polypeptide, or a polysaccharide.

24. (withdrawn) The method of claim 22, wherein said bulky group comprises hyaluronic acid or alpha-1-acid glycoprotein.

25. (previously presented) The method of claim 22, wherein said bulky group comprises polyethylene glycol or N-hxg.

26. (cancelled).

27. (cancelled).

28. (previously presented) The method of claim 12, wherein said corticosteroid conjugate comprises a corticosteroid attached to a bulky group and said bulky group comprises a corticosteroid.

29. (previously presented) The method of claim 12, wherein said corticosteroid conjugate comprises a corticosteroid attached to a bulky group of greater than 600 daltons.

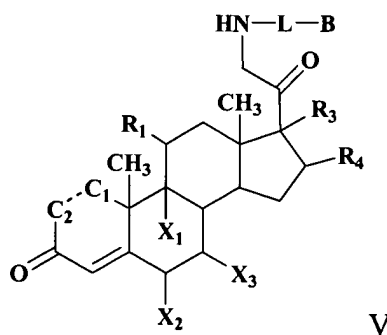
30. (previously presented) The method of claim 12, wherein said corticosteroid conjugate comprises a corticosteroid attached to a bulky group of greater than 800 daltons.

31. (previously presented) The method of claim 12, wherein said corticosteroid conjugate is resistant to *in vivo* cleavage, such that *in vivo* less than 5% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion.

32. (previously presented) The method of claim 12, wherein said corticosteroid conjugate is resistant to *in vivo* cleavage, such that *in vivo* less than 2% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion.

33. (previously presented) The method of claim 12, wherein said corticosteroid is selected from beclomethasone, budesonide, prednisolone, prednisone, and triamcinolone.

34. (withdrawn) The method of claim 12, wherein said corticosteroid conjugate is described by formula V:



wherein

the bond between C₁ and C₂ is a double or a single bond;

X₁ represents -H or a halogen atom;

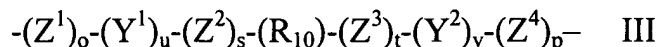
X₂ represents -H, -CH₃, or a halogen atom;

X₃ represents -H or a halogen atom;

R₁ represents =O or -OH;

R₃ and R₄ each, independently, represents -H, C₁₋₁₀ alkyl, -OH, or -O-acyl,

L is a linker described by formula III:



wherein

Z¹, Z², Z³, and Z⁴ each, independently, is selected from O, S, and NR₁₁;

R₁₁ is hydrogen or a C₁₋₁₀ alkyl group;

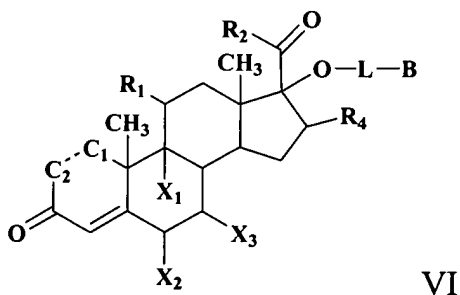
Y¹ and Y² are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

o, p, s, t, u, and v are each, independently, 0 or 1;

R₁₀ is a C₁₋₁₀ alkyl, a linear or branched heteroalkyl of 1 to 10 atoms, a linear or branched C₂₋₁₀ alkene, a linear or branched C₂₋₁₀ alkyne, a C₅₋₁₀ aryl, a cyclic system of 3 to 10 atoms, -(CH₂CH₂O)_qCH₂CH₂- in which q is an integer of 1 to 4, or a chemical bond linking -(Z¹)_o-(Y¹)_u-(Z²)_s- to -(Z³)_t-(Y²)_v-(Z⁴)_p-; and

B is either a bulky group of greater than 400 daltons or a charged group of less than 400 daltons.

35. (withdrawn) The method of claim 12, wherein said corticosteroid conjugate is described by formula VI:



wherein

the bond between C₁ and C₂ is a double or a single bond;

X₁ represents -H or a halogen atom;

X₂ represents -H, -CH₃, or a halogen atom;

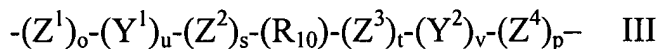
X₃ represents -H or a halogen atom;

R₁ represents =O or -OH;

R₂ represents -CH₃, -SCH₂F, -CH₂Cl, -CH₂OH, -CH₂O-P(O)(O⁻)₂, or CH₂O-acyl;

R₄ represents -H, C₁₋₁₀ alkyl, -OH, or -O-acyl;

L is a linker described by formula III:



wherein

Z¹, Z², Z³, and Z⁴ each, independently, is selected from O, S, and NR₁₁;

R₁₁ is hydrogen or a C₁₋₁₀ alkyl group;

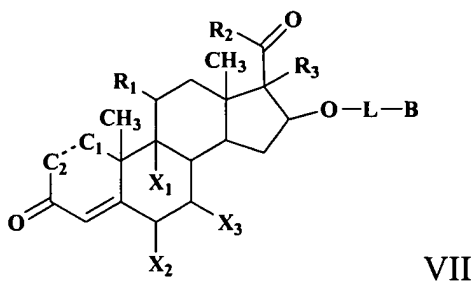
Y¹ and Y² are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

o, p, s, t, u, and v are each, independently, 0 or 1;

R₁₀ is a C₁₋₁₀ alkyl, a linear or branched heteroalkyl of 1 to 10 atoms, a linear or branched C₂₋₁₀ alkene, a linear or branched C₂₋₁₀ alkyne, a C₅₋₁₀ aryl, a cyclic system of 3 to 10 atoms, -(CH₂CH₂O)_qCH₂CH₂- in which q is an integer of 1 to 4, or a chemical bond linking -(Z¹)_o-(Y¹)_u-(Z²)_s- to -(Z³)_t-(Y²)_v-(Z⁴)_p-; and

B is either a bulky group of greater than 400 daltons or a charged group of less than 400 daltons.

36. (withdrawn) The method of claim 12, wherein said corticosteroid conjugate is described by formula VII:



wherein

the bond between C₁ and C₂ is a double or a single bond;

X₁ represents -H or a halogen atom;

X₂ represents -H, -CH₃, or a halogen atom;

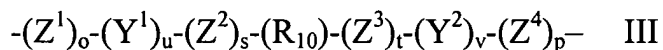
X₃ represents -H or a halogen atom;

R₁ represents =O or -OH;

R₂ represents -CH₃, -SCH₂F, -CH₂Cl, -CH₂OH, -CH₂O-P(O)(O⁻)₂, or CH₂O-acyl;

R₃ represents -H, C₁₋₁₀ alkyl, -OH, or -O-acyl;

L is a linker described by formula III:



wherein

Z¹, Z², Z³, and Z⁴ each, independently, is selected from O, S, and NR₁₁;

R₁₁ is hydrogen or a C₁₋₁₀ alkyl group;

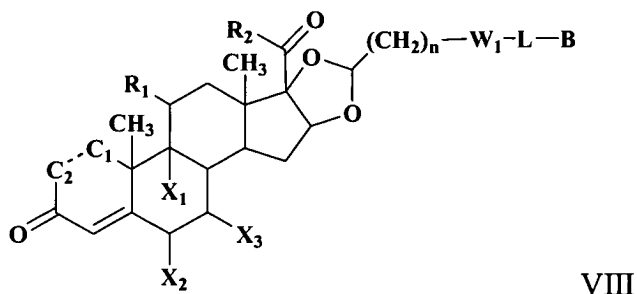
Y¹ and Y² are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

o, p, s, t, u, and v are each, independently, 0 or 1;

R₁₀ is a C₁₋₁₀ alkyl, a linear or branched heteroalkyl of 1 to 10 atoms, a linear or branched C₂₋₁₀ alkene, a linear or branched C₂₋₁₀ alkyne, a C₅₋₁₀ aryl, a cyclic system of 3 to 10 atoms, -(CH₂CH₂O)_qCH₂CH₂- in which q is an integer of 1 to 4, or a chemical bond linking -(Z¹)_o-(Y¹)_u-(Z²)_s- to -(Z³)_t-(Y²)_v-(Z⁴)_p-; and

B is either a bulky group of greater than 400 daltons or a charged group of less than 400 daltons.

37. (withdrawn) The method of claim 12, wherein said corticosteroid conjugate is described by formula VIII:



wherein

the bond between C₁ and C₂ is a double or a single bond;

X₁ represents -H or a halogen atom;

X₂ represents -H, -CH₃, or a halogen atom;

X₃ represents -H or a halogen atom;

R₁ represents =O or -OH;

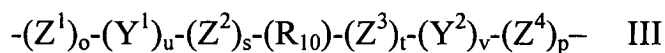
R₂ represents -CH₃, -SCH₂F, -CH₂Cl, -CH₂OH, -CH₂O-P(O)(O⁻)₂, or CH₂O-acyl;

n is an integer from 0 to 6;

W₁ represents -NR₈-, -NH-NH-, -O-, -S-, -C(O)-, or -C(S)-;

R₈ represents -H, C₁₋₁₀ alkyl or C₅₋₁₀ aryl;

L is a linker described by formula III:



wherein

Z¹, Z², Z³, and Z⁴ each, independently, is selected from O, S, and NR₁₁;

R₁₁ is hydrogen or a C₁₋₁₀ alkyl group;

Y¹ and Y² are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;

o, p, s, t, u, and v are each, independently, 0 or 1;

R₁₀ is a C₁₋₁₀ alkyl, a linear or branched heteroalkyl of 1 to 10 atoms, a linear or

branched C₂₋₁₀ alkene, a linear or branched C₂₋₁₀ alkyne, a C₅₋₁₀ aryl, a cyclic system of 3 to 10 atoms, -(CH₂CH₂O)_qCH₂CH₂- in which q is an integer of 1 to 4, or a chemical bond linking -(Z¹)_o-(Y¹)_u-(Z²)_s- to -(Z³)_t-(Y²)_v-(Z⁴)_p-; and

B is either a bulky group of greater than 400 daltons or a charged group of less than 400 daltons.